



BRIEF REPORT

# Safety of Biologic Therapies in Patients with Moderate-to-Severe Plaque Psoriasis and Concomitant Viral Hepatitis: A Monocentric Retrospective Study

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## ABSTRACT

**Introduction:** There are no strong data regarding the treatment with biologics (especially for the most recent anti-IL-17 and anti-IL-23 drugs) of patients with psoriasis and concomitant viral hepatitis. We assessed the safety of biologic drugs in patients with psoriasis who are seropositive for hepatitis B or C and did not receive antiviral prophylaxis.

**Methods:** We conducted a retrospective single-center study. The efficacy of biologic treatments was evaluated by assessing the Psoriasis Area and Severity Index (PASI) score during all visits, for a minimum follow-up of 52 weeks. All patients were evaluated by a hepatologist before starting the treatment. They were monitored for reactivation of viral hepatitis.

**Results:** Twenty patients had positive markers of hepatitis B virus (HBV) or hepatitis C virus (HCV). Seventeen patients had positive markers of HBV infection, and four patients had antibodies for HCV (one patient had serologic evidence of both infections). Anti-IL-23 biologics were the most used in our population, with risankizumab being the most prescribed drug. No patient had evidence of viral reactivation during our study. Study limitations include its retrospective nature and our inclusion of patients with different serological status receiving different biologic drugs.

**Conclusion:** Biologic therapies (including anti-IL-23 drugs) appear to be safe in patients seropositive for HCV or HBV core antibody who did not receive antiviral prophylaxis.

**Keywords:** Anti-IL-17; Anti-IL-23; Biologics; Hepatitis B virus; Hepatitis C virus; Psoriasis; Reactivation

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### Key Summary Points

Biologics appear to be safe in patients with psoriasis who are seropositive for viral hepatitis, but not enough data are available, especially regarding anti-IL-17 and anti-IL-23 drugs.

Drug resistance due to the use of prophylactic antivirals is an increasing concern.

In our experience, despite not receiving prophylaxis, no patient had evidence of viral reactivation during the treatment, supporting the high safety profiles of biologic drugs.

Biologics, including anti-IL-17 and anti-IL-23, appear to be a safe therapeutic option in patients with serological evidence of viral hepatitis with a follow-up of at least 52 weeks.

Longer studies with larger cohorts of patients are needed to further assess this subject.

## INTRODUCTION

Psoriasis is a chronic skin disease that affects about 2–4% of the world population [1]. Typically, psoriasis presents with erythematous and scaly plaques and patches diffused to the trunk and to upper and lower limbs. Frequently, plaque psoriasis can also involve scalp, palms/soles, genitals, and nails, significantly impairing patients' quality of life. It is now well known that psoriasis also plays a crucial role in the development of different types of comorbidities, including psoriatic arthritis (PsA), cardiovascular diseases, arterial hypertension, and metabolic syndrome [2]. Biologic drugs have changed the management of moderate-to-

severe chronic plaque psoriasis with their effectiveness and safety profiles, and they appear also to have an impact on the natural history of this disease [3]. However, there is a lack of strong evidence regarding the treatment with biologics (especially for the most recent anti-IL-17 and anti-IL-23 drugs) of patients with concomitant viral hepatitis B or C. These more recent biologics treatments appear to have better safety profiles, based on data from both randomized clinical trials and real-life experiences [4, 5]. On the other hand, several reports suggest that anti-TNF- $\alpha$  monoclonal antibodies should be avoided in those patients because of the higher risk of serious infections compared with nonbiologic therapies [6].

In the absence of clear evidence, most clinicians decide to prescribe prophylaxis with lamivudine or other antiviral drugs before starting therapy in patients with evidence of viral hepatitis B. On the other hand, drug resistance due to the use of prophylactic antivirals is increasingly developing, raising concerns about their overuse [7].

The aim of this retrospective real-life single center study is to assess the efficacy and the safety of biologic drugs in a cohort of 20 patients affected by severe plaque type psoriasis and concurrent chronic viral hepatitis (both chronic inactive hepatitis and occult cases) with no clinical signs and/or lab indication of active liver disease) who did not receive antiviral prophylaxis before starting treatment.

## METHODS

This is a non-interventional retrospective single-center real-life study analyzing the psoriasis database of our dermatology department.

The inclusion criteria are:

1. Male or female patients 18 years old or more
2. Patients being treated for at least 52 weeks with biologic drugs for moderate-to-severe psoriasis (with or without psoriatic arthritis)
3. Laboratory findings of chronic HBV infection or occult cases, without any clinical or

laboratory sign of active chronic hepatitis at the routine screening examinations [including hepatitis B surface antibody (anti-HBs), core antibody (anti-HBc), surface antigen (HBsAg)]

- Occult HBV infection was defined for patients with negative HBsAg, negative HBsAb, and positive anti-HBcAb
  - Chronic HBV infection was defined by presence of positive HBsAg
  - Resolved past HBV infection was defined as negative HBsAg, with positive HBsAb and HBcAb
4. Patients with positive antibodies for HCV, regardless of the presence of detectable HCV-RNA

Moderate-to-severe psoriasis was defined by the “rule of 10” before starting biologic therapies [PASI > 10, Body Surface Area (BSA) > 10 or Dermatology Life Quality Index (DLQI) > 10] [8]. The efficacy of biologic treatments was defined by assessing Psoriasis Area and Severity Index (PASI) during all visits. All patients were evaluated by a hepatologist and underwent testing for viral load before obtaining approval to start biologic treatment. According to the hepatologist’s indications, patients were regularly monitored for reactivation of viral hepatitis with liver enzymes, viral DNA load and viral RNA load (for HBV and HCV viruses, respectively), and viral markers (every 3 months). They also underwent periodical hepatologic visits. None of our patients received antiviral therapies before the start of the biologic drug.

Active hepatitis was defined as transaminases enzyme elevation at least five times the upper normal limit [9]. HBV reactivation was defined as an increase in HBV replication of > 1 log<sub>10</sub> copies/mL or seroconversion from negative to positive HBsAg [9].

Institutional review board approval was exempted as the study protocol did not deviate from standard clinical practice. All included patients had provided written consent for retrospective study of data collected during routine clinical practice.

## RESULTS

Of the 794 patients with psoriasis or psoriatic arthritis treated with a biologic drug at our department, 20 (2.52%) patients had positive markers of HBV or HCV before starting the treatment. Seventeen patients had positive markers of HBV infection and four patients had positive antibodies for HCV, but HCV-RNA was undetectable in all patients (one patient had serologic evidence of both HBV and HCV infection).

Regarding patients with HBV infection, 12 were male (70.59%) and 5 were female (29.41%). All were affected by plaque psoriasis, and their median age was 57 years. Four patients received more than one biologic drug. Anti-IL-23 biologics were the most used in our population, with risankizumab being the most prescribed drug ( $n = 11$ ), followed by tildrakizumab, ustekinumab, ixekizumab, secukinumab ( $n = 2$  each), brodalumab, adalimumab, and etanercept ( $n = 1$  each). Median PASI at baseline was 15. Two patients were also affected by psoriatic arthritis, and the most common comorbidity was arterial hypertension ( $n = 8$ ), followed by type 2 diabetes ( $n = 2$ ). All patients were followed through at least 52 weeks, with six patients completing at least 2 years of treatment. Five patients had a serologic status suggestive for a previous resolved HBV infection (with negative HbsAg and positive HbsAb and HbcAb), while 11 patients had a positivity for HbcAb only. Just one patient was an inactive HBV carrier, with positive HbsAg (256,66 mIU/mL), negative antibodies, and undetectable viral load (Table 1). No patient received the indication of prophylaxis from our hepatologists. During follow-up, each patient underwent blood testing for HBV viral load and HbsAg, along with transaminases, every 3 months for the first year of therapy and then every 6 months. No patient had evidence of viral reactivation during our study. At the last available observation, PASI 100 was achieved by 12 patients (70.59%), while 15 patients (88.24%) maintained a PASI 90 response, at least (Table 1). To date, all patients are still under treatment with a biologic drug, as none of them

**Table 1** Clinical and laboratory characteristics of patients with HBV infection

Patient number	Sex	Age group	Comorbidities	HbsAg (mIU/mL)	HbsAb	HbcAb	HBV-DNA	Biologic therapies	Follow-up duration (weeks)	PASI baseline	PASI at last observation
1	M	40–44	/	256.66	19.19	Negative	Undetectable	Risankizumab	104	16	0
2	M	55–69	DM2, hypertension	Negative	Positive	Positive	Undetectable	Ustekinumab	52	12	5
3	M	65–69	DM2, NASH	Negative	Negative	Positive	Undetectable	Risankizumab	52	10	1
4	M	50–54	HCVab <sup>+</sup>	Negative	< 1	Positive	Undetectable	Risankizumab	52	15	0
5	M	55–59	Hypertension, NAFLD	Negative	Negative	Positive	Undetectable	Tildrakizumab	52	25.5	0
6	F	55–59	Hypertension	Negative	Negative	Positive	Undetectable	Risankizumab	52	12	0
7	M	50–54	Metabolic syndrome	Positive	Negative	Positive	Undetectable	Risankizumab	52	20	10
8	M	65–69	Previous bladder carcinoma	Negative	Negative	Positive	Undetectable	Etanercept, risankizumab	208	32	0
9	M	55–59	PsA	Negative	Negative	Positive	Undetectable	Adalimumab, ixekizumab	208	18	0
10	M	55–59	/	Negative	Negative	Positive	Undetectable	Secukinumab	104	18	0.3
11	F	65–69	PsA, hypertension	Negative	Negative	Positive	Undetectable	Guselkumab, ixekizumab	52	10	1
12	M	55–59	Hypercholesterolemia	Negative	211	Positive	Undetectable	Tildrakizumab	52	12	0
13	F	70–74	Hypertension	Negative	Positive	Positive	Undetectable	Risankizumab	52	28	0
14	F	55–59	Hypertension, NASH	Negative	Positive	Positive	Undetectable	Risankizumab	88	10	0
15	M	70–74	Hypertension, QuantiFERON positive	Negative	Negative	Positive	Undetectable	Risankizumab	128	15	0
16	M	45–49	Hypertension, OSAS	Negative	Negative	Positive	Undetectable	Ustekinumab, risankizumab	140	17	0

**Table 1** continued

Patient number	Sex	Age group	Comorbidities	HbsAg (mIU/mL)	HbsAb	HbcAb	HBV-DNA	Biologic therapies	Follow-up duration (weeks)	PASI baseline	PASI at last observation
17	M	60–64	/	Negative	Positive	Positive	Undetectable	Secukinumab, brodalumab	128	10	0

HBV hepatitis B virus, HbsAg HBV surface antigen, HbsAb HBV surface antibody, HbcAb HBV core antibody

has experienced neither adverse events leading to discontinuation nor therapeutic ineffectiveness.

Four patients had serological evidence of HCV infection (three men and one woman), with a median age of 54.5 years (Table 2). Viral HCV load was undetectable for all of them. All patients were followed for at least 52 weeks. One patient was treated with ustekinumab for more than 4 years, another patient received risankizumab, achieving a PASI 100 response. The third patient also reached PASI 100 during treatment with ixekizumab. The fourth patient, who also had a diagnosis of PsA, was treated with adalimumab, before being switched to secukinumab and then to brodalumab, achieving good control of both psoriasis and PsA. Each patient was tested for HCV-RNA every 3 months, and none of them showed sign of viral reactivation.

## DISCUSSION

Since biologic therapies are becoming the standard of care for the treatment of moderate-to-severe plaque psoriasis, it is very important to assess the safety of these drugs in patients with serology suggestive for viral hepatitis. Reports regarding the safety profile of biologic drugs in patients affected by viral hepatitis show contrasting data. However, the vast majority of these studies focused on anti-TNF- $\alpha$  drugs and ustekinumab, and those studies included mostly patients with rheumatic diseases [10].

Regarding viral hepatitis B, none of our patients (including the one individual with positive HbsAg) experienced viral reactivation despite not receiving antiviral prophylaxis, supporting the safety of biologics in this population. Although the risk of HBV reactivation during the course of biologic therapy is considered to be low, especially for HbsAg-negative patients, it is relevant to underline that viral load was persistently undetectable in all patients in our experience, strongly decreasing the risk of a possible viral reactivation. A retrospective study by Sanz-Bueno et al. [11] on 20 patients treated for psoriasis with a TNF inhibitor or ustekinumab, having evidence of prior

**Table 2** Clinical and laboratory characteristics of patients with evidence of previous HCV infection

Patient number	Sex	Age	Comorbidities	HCV-ab	HCV-RNA	Biologic therapies	Follow-up duration (weeks)	PASI baseline	PASI at last observation
1	F	50–54	Hypertension, obesity	Positive	Undetectable	Ustekinumab	220	30	5
2	M	50–54	HBcAb <sup>+</sup>	Positive	Undetectable	Risankizumab	52	15	0
3	M	55–59	Hypertension, CVD	Positive	Undetectable	Ixekizumab	52	18	0
4	M	60–64	PsA	Positive	Undetectable	Adalimumab, secukinumab, brodalumab	104	10	1

*HBV-ab* antibody to HCV

infection with hepatitis B (defined as the positivity for anti-HBc, the absence of HBsAg, and the presence or absence of anti-HBs), did not report any case of hepatitis B reactivation. As in our experience, none of the patients received prophylaxis before starting treatment. A study by Viganò et al. [12] recommended HBV prophylaxis in patients with positive HBsAg before therapy with anti-TNF drugs, while they agreed that patients seropositive for anti-HBc should be closely monitored. In our study, we found the presence of HbsAg in only two patients: they were both treated with risankizumab after a hepatologic visit, which recommended only monitoring for reactivation of viral hepatitis with liver enzymes and viral DNA load testing. In a systematic review by Snast et al. [13], only 1.14% (2/175) of patients with positive HbcAb had viral reactivation. Regarding patients with chronic HBV infection (positive HbsAg regardless of serological status), reactivation was experienced by 3/26 patients (11.54%) receiving prophylaxis compared with 5/14 (35.71%) patients without prophylaxis. This review included 312 patients with evidence of hepatitis B, all treated with either ustekinumab or anti-TNF- $\alpha$  therapies [13]. According to a review article by Kaushik and Lebwohl [14], biologic therapy can be initiated in all patients affected by chronic (or past) infection from hepatitis B, under close laboratory and clinical monitoring with a hepatologist. According to their experience, IL-17 inhibitors appear safe if used after antiviral prophylaxis in patients with positive HbsAg, while no data were reported on anti-IL-23 drugs. On the other hand, they approved the use of anti-TNF- $\alpha$ , ustekinumab, and anti-IL-17 in patients with positive HbcAb. No data were available on anti-IL-23 treatments in this population.

Regarding chronic HCV infection, the risk of reactivation in patients with positivity for HCV-ab but undetectable HCV-RNA is considered to be very low [13]. Moreover, several studies have demonstrated that TNF- $\alpha$  inhibitors are associated with a decrease in viral load. The previously mentioned review by Snast et al. [13] reports a yearly rate of viral reactivation of 2.42% in patients treated with either adalimumab or etanercept. According to Kaushik



and Lebwohl [14], regarding biologic therapies, IL-17 inhibitors and apremilast appear to have a favorable safety profile, while patients receiving TNF- $\alpha$  inhibitors should receive antiviral therapy and be monitored closely. However, in their review, only limited data on IL-23 inhibitors were available. Our study included only four patients, and none of them experienced viral reactivation during the course of therapy.

Our study has several limitations, the first being its retrospective nature, which does not allow us to generalize our conclusions. Second, a follow-up of 52 weeks may be too short to assess the safety profile of biologics in our population, despite half of our patients reaching at least 104 weeks of observation. Moreover, we included patients with different serological status receiving different biologic drugs, which may make it difficult to generalize our data. However, our retrospective study has the particularity of including only patients treated with anti-IL-12/23, anti-IL-17, or anti-IL-23 therapies, which now represent the standard of care for moderate-to-severe plaque psoriasis.

## CONCLUSION

In conclusion, our data show that none of our patients experienced reactivation of viral hepatitis, during treatment with anti-IL12/23, anti-IL-17, and anti-IL-23 biologic drugs for at least 52 weeks, despite not receiving antiviral prophylaxis. Since no strong evidence is available yet, we recommend strict monitoring for HbsAg and HBV/HCV viral load during the course of therapy with biologics for psoriasis. Further prospective studies, with larger cohorts of patients and longer follow-up periods, are needed to assess the risk of viral reactivation in patients receiving biologic therapies.

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**Disclosures.** Antonio Costanzo has been a consultant and/or speaker for Abb-Vie, Almirall, Amgen, Janssen, Leo Pharma, Eli Lilly, Galderma, Boehringer, Novartis, Pfizer, Sandoz, and UCB. Alessandra Narcisi has been a consultant and/or speaker for Abb-Vie, Almirall, Amgen, Janssen, Leo Pharma, Eli Lilly, Boehringer, Novartis, Pfizer and UCB. Luigi Gargiulo, Giulia Pavia, Mario Valenti, Ana Lleo de Nalda and Chiara Perugini have nothing to disclose.

**Compliance with Ethics Guidelines.** Institutional review board approval was exempted as the study protocol did not deviate from standard clinical practice. All included patients had provided written consent for retrospective study of data collected during routine clinical practice.

**Data Availability .** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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